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ORIGINAL ARTICLE

# Autoimmune skin disorders and SARS-CoV-2 vaccination – a meta-analysis

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## Summary

**Background and objectives:** The coronavirus SARS-CoV-2, which is the cause of COVID-19 disease in infected patients, has led to an ongoing worldwide pandemic. Although SARS-CoV-2 vaccination had a dramatic positive effect on the course of COVID-19, there has been increasing evidence of adverse effects after SARS-CoV-2 vaccination. This meta-analysis highlights the association between SARS-CoV-2 vaccination and *de novo* induction or aggravation of inflammatory and autoimmune skin diseases.

**Material and methods:** A systematic meta-analysis of the literature on new onset or worsening of inflammatory and autoimmune diseases after SARS-CoV-2 vaccination was performed according to the PRISMA guidelines. The search strategy included following terms: "COVID-19/SARS-CoV-2 vaccine bullous pemphigoid/pemphigus vulgaris/systemic lupus erythematosus/dermatomyositis/lichen planus/leukocytoclastic vasculitis." Moreover, we describe representative cases from our dermatology department.

**Results:** The database-search in MEDLINE identified 31 publications on bullous pemphigoid, 24 on pemphigus vulgaris, 65 on systemic lupus erythematosus, nine on dermatomyositis, 30 on lichen planus, and 37 on leukocytoclastic vasculitis until June 30th, 2022. Severity and response to treatment varied among the described cases.

**Conclusions:** Our meta-analysis highlights a link between SARS-CoV-2 vaccination and new onset or worsening of inflammatory and autoimmune skin diseases. Moreover, the extent of disease exacerbation has been exemplified by cases from our dermatological department.

## INTRODUCTION

Since 2019, the SARS-CoV-2 virus has spread over the globe and has caused more than one million deaths worldwide.[1] Since then, researchers worldwide have tried to develop therapies and vaccines against SARS-CoV-2 virus.[1] By July 2021, 105 SARS-CoV-2 vaccines had reached the clinical development phase.[2] Currently, whole virus live attenuated or inactivated (Sinopharm, Sinovac), protein-based (Novavax), viral vector (AstraZeneca, Janssen) and nucleic acid vaccines (mRNA – Pfizer/BioNTech and Moderna) are being administered.[2] In December 2020, the two mRNA-based SARS-CoV-2 vaccines, BioNTech/Pfizer and Moderna, obtained authorization by the FDA and later on by EMA.[1] Since then, millions of people have been vaccinated with mRNA vaccines.[3] While mRNA-based vaccines represent a new way in developing vaccines, Jackson, et al. had already introduced the concept of viral-based vaccine in 1972.[4] The SARS-CoV-2 vaccine developed by Janssen-Cilag and AstraZeneca is an adenoviral vector-based vaccine that has been widely used for immunization.[4] Although vaccination saved millions of lives worldwide, the association between

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**TABLE 1** Meta-analysis of bullous pemphigoid after SARS-CoV-2 vaccination.

| Vaccination | Vaccine type | Ø Days until flare | New-onset diagnosis (number of patients) | Pre-existing diagnosis (number of patients) | Total patients |
|---|---|---|---|---|---|
| First | mRNA | 5 | 9 | 4 | 13 |
| | AstraZeneca | 6 | 3 | – | 3 |
| | Others | 7 | – | 1 | 1 |
| Second | mRNA | 2 | 2 | – | 2 |
| | Others | 11 | 1 | 1 | 2 |
| Third | mRNA | 10 | 5 | 2 | 7 |
| Data without further information | mRNA | ? | ? | ? | 37 |
| | AstraZeneca | ? | ? | ? | 1 |

Based on MEDLINE until the 30th of June 2022 with searching terms "COVID-19 vaccine bullous pemphigoid" and "SARS-CoV-2 vaccine bullous pemphigoid."

vaccination and development of autoimmune diseases is still under debate.[5] Indeed, new onset or worsening of autoimmune diseases after SARS-CoV-2 vaccination have been increasingly reported.[6,7]

In this paper, we present a meta-analysis of six dermatological diseases, which developed *de novo* or worsened after SARS-CoV-2 vaccination. In our analysis, we focused on the most common vaccines, such as mRNA-based vaccines (Pfizer/BioNTech and Moderna), AstraZeneca, and Janssen. Less commonly used SARS-CoV-2 vaccines in the Western hemisphere, such as Sinopharm, Sinovac, and Covavax, are grouped together under the term "others." Also However, in some cases it was not clear which SARS-CoV-2 vaccine was used or which vaccination was involved. These data were summarized under "Data without further information."

Specifically, we focused on worsening of pre-existing or new-onset diseases up to 21 days after SARS-CoV-2 vaccination, to reduce the likelihood of new diagnoses or worsening diseases occurring independently of vaccination.

## MATERIAL AND METHODS

A systematic meta-analysis of the literature about new onset or worsening of inflammatory and autoimmune disorders after SARS-CoV-2 vaccination was performed according to PRISMA guidelines. MEDLINE was systematically searched until June 30th, 2022. The search strategy included following terms: "COVID-19/SARS-CoV-2 vaccine bullous pemphigoid/pemphigus vulgaris/systemic lupus erythematosus/dermatomyositis/lichen planus/leukocytoclastic vasculitis." All terms were used to search titles and abstracts of publications. The papers were independently reviewed by two authors: Julia Hinterseher (JH) and Michael Hertl (MH). A third independent reviewer (Dario Didona [DD]) decided in case of discrepancy. New cases and worsening of pre-existing diseases with a temporal relation to SARS-CoV-2 vaccination were included in this meta-analysis. Non-English articles and congress abstracts were excluded. Moreover, we described representative cases from our dermatological department.

## RESULTS

### Bullous pemphigoid

The database-search in MEDLINE identified 31 publications. Overall, 66 cases were included (Table 1). Excluding the subset "Data without further information" (Table 1), a new onset or worsening was found in 28 published cases of bullous pemphigoid (BP) after SARS-CoV-2 vaccination. Of these 28 patients, a new onset was reported in 20 patients (approximately 70%), while a worsening of pre-existing BP was seen in eight patients (approximately 30%). The interval between SARS-CoV-2 vaccination and worsening/new onset of BP ranged between eight and 11 days.

We also observed a worsening or a new onset of BP in our outpatient clinic after SARS-CoV-2 vaccination in three patients. A 66-year-old male patient showed multiple tense blisters, mainly on the feet and dorsa of the hands (Figure 1). Approximately three weeks before the onset of the blisters, he received the first SARS-CoV-2 vaccination with mRNA-based vaccine (Pfizer/BioNTech). The diagnosis of BP was established by histopathology (subepidermal cleft), and direct immunofluorescence (DIF) with linear deposits of IgG along the basement membrane zone (BMZ). Serum IgG autoantibodies against BP180 were detected by ELISA (66 RE/ml). The patient showed a dramatic improvement after topical therapy with high-potency steroids. After the booster vaccination, he developed a BP flare.

A 67-year-old male patient developed BP three years before SARS-CoV-2 vaccination. He developed pruritic skin lesions one week after the first vaccination with the SARS-CoV-2 vaccine Vaxzevria (AstraZeneca). After a temporary improvement on topical therapy with high-potency steroids and systemic doxycycline, the patient experienced a new flare two weeks after the second booster with mRNA

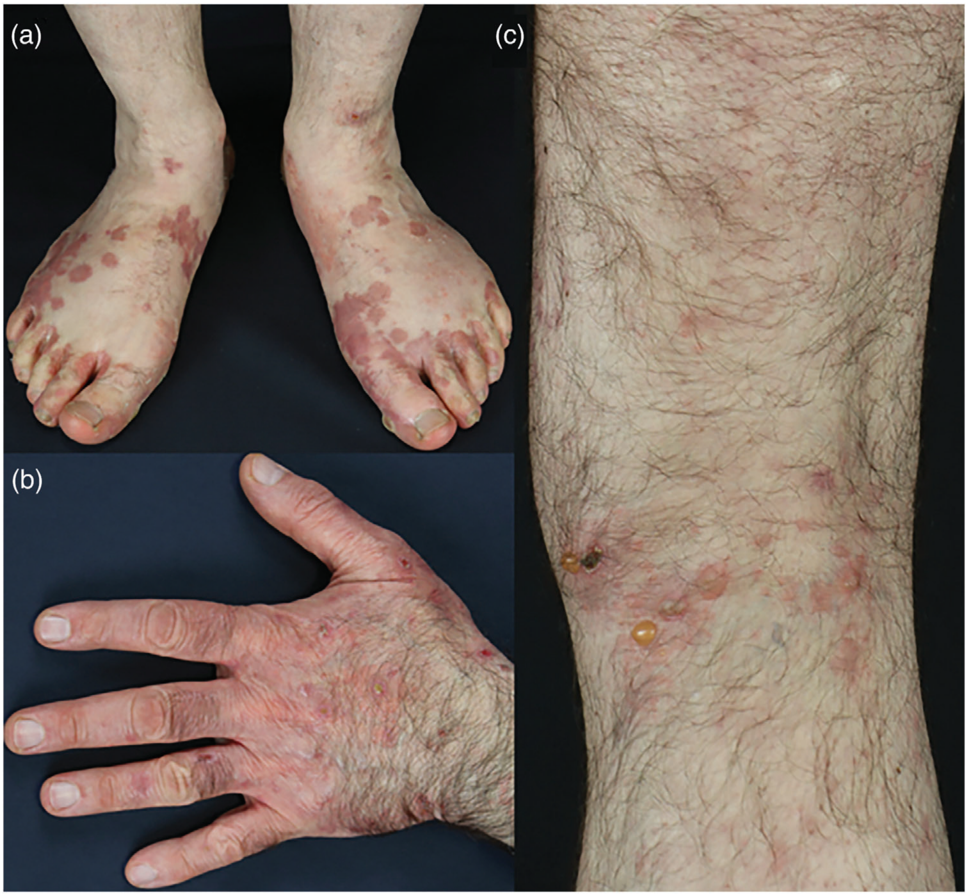

**FIGURE 1** New onset of bullous pemphigoid circa three weeks after mRNA-based SARS-CoV-2 vaccination. (a) Erythematous patches on both feet with a single tense blister on the link foot. (b) Erythematous patches with superficial erosions on the left hand. (c) Tense blisters on erythematous skin on the left calf.

vaccine (Pfizer/BioNTech) (Figure 2). The patient was treated with glucocorticoid pulse therapy and topical therapy with high-potency steroids.

A 61-year-old female patient with BP was already vaccinated twice with mRNA-based vaccine (Pfizer/BioNTech). After the third SARS-CoV-2 vaccination, she showed a flare of BP, with multiple tense blisters all over her body. After a topical therapy with high-potency steroids, she showed a clinical improvement.

## Pemphigus vulgaris

The database-search in MEDLINE identified 24 publications with 14 cases of a new onset or worsening of pemphigus vulgaris (PV) after SARS-CoV-2 vaccination (Table 2). Among them, eight patients (approximately 57%) had a new onset of PV after SARS-CoV-2 vaccination and six patients (approximately 43%) experienced a worsening of a previously diagnosed PV. The interval between SARS-CoV-2 vaccination and the worsening/new onset of PV varied between five and 16 days.

Here, we describe a 36-year-old female patient who had a flare of a previously diagnosed PV seven days after the third SARS-CoV-2 mRNA-based vaccination (Pfizer/BioNTech). She developed bilateral buccal erosions (Figure 3). The diagnosis of PV was confirmed by histopathology (suprabasal epidermal loss of adhesion) and epidermal cell surface deposits of IgG and C3 by DIF. In addition, IgG serum autoantibodies against desmoglein 3 were detected by ELISA (125 RE/ml). The patient showed a massive clinical improvement on oral prednisolone (15 mg/day) and mycophenolate mofetil (2 g/day).

## Systemic lupus erythematosus

The database-search in MEDLINE identified 65 publications and a total of 51 cases (Table 3). Excluding the subset "Data without further information" (Table 3), we found a new onset or worsening in 11 published cases of systemic lupus erythematosus (SLE) after SARS-CoV-2 vaccination. Among them, in seven patients the diagnosis of SLE was de novo established (approximately 64%), while a worsening of a previously diagnosed SLE was reported in four patients (approximately 36%). The interval between SARS-CoV-2 vaccination and the new onset/worsening of SLE was between four and 11 days.

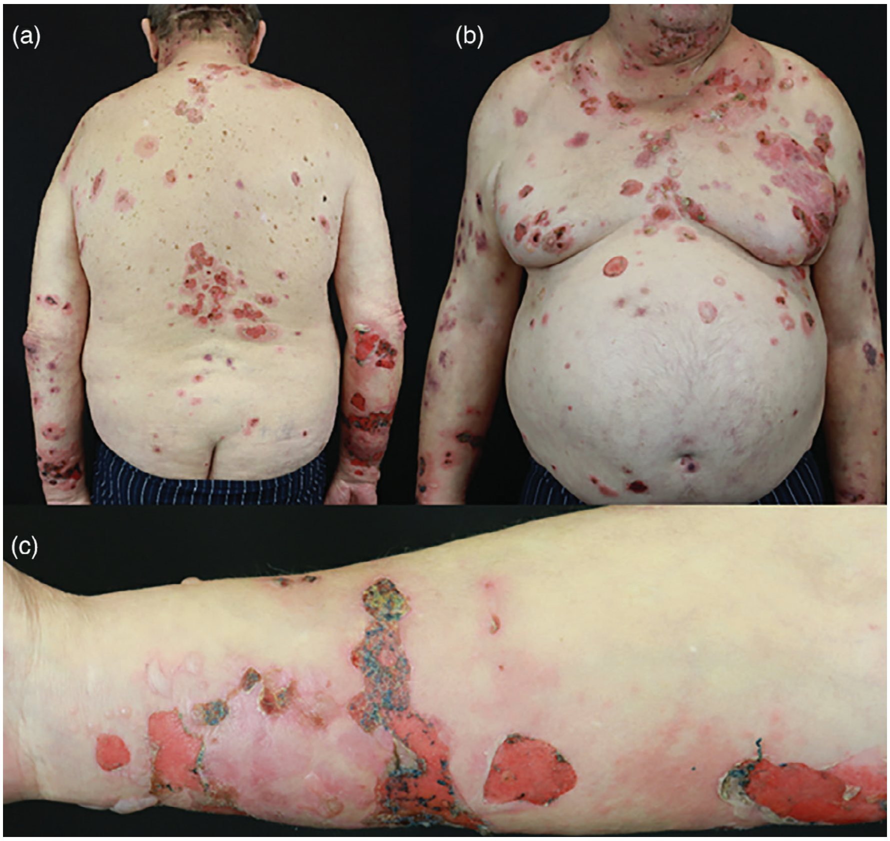

**FIGURE 2** Worsening of a previously diagnosed bullous pemphigoid after the second SARS-CoV-2 booster vaccination with mRNA-based vaccine. Multiple erosions and tense blisters on erythematous skin (a) on the back, (b) on the chest, and (c) on the right forearm.

**TABLE 2** Meta-analysis of pemphigus vulgaris after SARS-CoV-2 vaccination.

| Vaccination | Vaccine type | ø Days until flare | New-onset diagnosis (number of patients) | Pre-existing diagnosis (number of patients) | Total patients |
|---|---|---|---|---|---|
| First | mRNA | 5 | 1 | 5 | 6 |
| | AstraZeneca | 7 | 1 | – | 1 |
| Second | mRNA | 13 | 3 | – | 3 |
| | AstraZeneca | 7 | 1 | – | 1 |
| | Others | 14 | 2 | 1 | 3 |

Based on MEDLINE until the 30th of June 2022 with searching terms "COVID-19 vaccine pemphigus vulgaris" and "SARS-CoV-2 vaccine pemphigus vulgaris."

We also observed a worsening of a previously diagnosed SLE after the fourth SARS-CoV-2 mRNA-based vaccination (Pfizer/BioNTech). A 60-year-old male patient developed new erythematous skin lesions and worsening of arthritis shortly after the second booster mRNA vaccination (Pfizer/BioNTech).

## Dermatomyositis

The database-search in MEDLINE identified nine publications and a total of 25 cases (Table 4). Excluding the subset "Data without further information", we found a new onset in eight published cases of dermatomyositis (DM) after SARS-CoV-2 vaccination. The time interval from SARS-CoV-2 vaccination to new-onset disease varied between one and eight days.

Here, we describe the worsening of a previously diagnosed DM in one patient and a case of new onset of DM after SARS-CoV-2 vaccination. A 48-year-old female patient experienced a flare of DM after the third Pfizer (BioNTech) SARS-CoV-2 vaccination, complaining of muscular pain and weakness. A diagnosis of DM had been established five years earlier and she had been treated for two years with azathioprine (AZA). Later, the therapy was stopped due to complete recovery of skin and muscular symptoms.

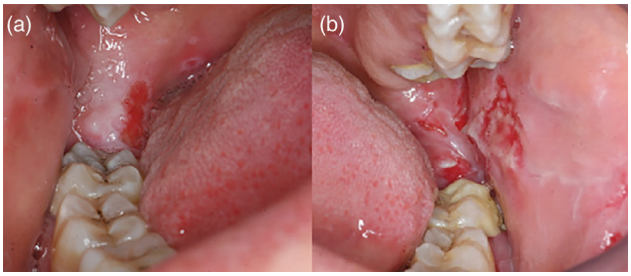

**FIGURE 3** Worsening of a previously diagnosed pemphigus vulgaris after the third mRNA-based SARS-CoV-2 vaccination. (a, b) Multiple erosions of the oral mucosa.

Because of worsening of DM after Pfizer (BioNTech) vaccination, she was treated again with AZA, showing a massive clinical improvement after six weeks.

The second patient, a 75-year-old female, was admitted to our clinic because of pain and severe weakness of the proximal muscles one week after the second Pfizer (BioNTech) vaccination. She also showed Gottron papules on both hands and nail fold hyperkeratosis (Keining's sign). In addition, a heliotrope erythema of the face, décolleté (V sign), and thighs (Holster sign) was observed (Figure 4). Histological findings were compatible with DM. Serologically, IgG serum antibodies against nuclear matrix protein 2 (NXP2) and Ro-52 were detected. Furthermore, a cecal carcinoma was detected by colonoscopy. Therefore, a diagnosis of paraneoplastic DM was established, those clinical development may have been accelerated by SARS-CoV-2 vaccination.

## Lichen planus

The database-search in MEDLINE identified 30 publications. Overall, we identified 19 cases of a new onset or worsening of lichen planus (LP) after SARS-CoV-2 vaccination (Table 5). Excluding the subset "Data without further information" (Table 5), 15 individual cases were found. In 12 cases (80%), a new onset of LP occurred after SARS-CoV-2 vaccination. In two cases, the new onset of LP was limited only to skin areas affected previously by vitiligo. Furthermore, three patients (20%) showed a worsening of LP after SARS-CoV-2 vaccination. The time interval between SARS-CoV-2 vaccination and new onset/worsening of LP ranged from five to 14 days.

In a 58-year-old male patient, the diagnosis of LP was established 14 years before vaccination with Pfizer (BioNTech). A few days later, the patient developed lichenoid papules, which initially did not respond to topical therapy with corticosteroids. Therefore, a therapy with acitretin was started, which led to a rapid clinical improvement.

A 53-year-old female patient had been diagnosed with LP follicularis three years before vaccination. After the third SARS-CoV-2 vaccination with Pfizer (BioNTech) she showed a significant worsening of the itching sensation on the scalp and hair loss. Furthermore, the patient complained of worsening of her undelying Crohn's disease.

## Leukocytoclastic vasculitis

The database-search in MEDLINE identified 37 publications. Finally, 31 cases were included (Table 6). Overall, 27 patients

**TABLE 3** Meta-analysis of systemic lupus erythematosus after SARS-CoV-2 vaccination.

| Vaccination | Vaccine type | ø Days till flare | New-onset diagnose (number of patients) | Pre-existing diagnose (number of patients) | Total patients |
|---|---|---|---|---|---|
| First | mRNA | 4 | 2 | 2 (Lupus Nephritis) | 4 |
| | AstraZeneca | 10 | 2 | 1 | 3 |
| Second | mRNA | 11 | 3 | 1 | 4 |
| Data without more information | mRNA | ? | ? | ? | 40 |

Based on MEDLINE until the 30th of June 2022 with searching terms "COVID-19 vaccine systemic lupus erythematosus" and "SARS-CoV-2 vaccine systemic lupus erythematosus"

**TABLE 4** Meta-analysis of dermatomyositis after SARS-CoV-2 vaccination.

| Vaccination | Vaccine type | ø Days until flare | New-onset diagnosis (number of patients) | Pre-existing diagnosis (number of patients) | Total patients |
|---|---|---|---|---|---|
| First | mRNA | 4 | 4 | – | 4 |
| Second | mRNA | 8 | 4 | – | 4 |
| Data without further information | mRNA | ? | ? | ? | 16 |
| | Janssen | ? | ? | ? | 1 |

Based on MEDLINE until the 30th of June 2022 with searching terms "COVID-19 vaccine dermatomyositis" and "SARS-CoV-2 vaccine dermatomyositis."

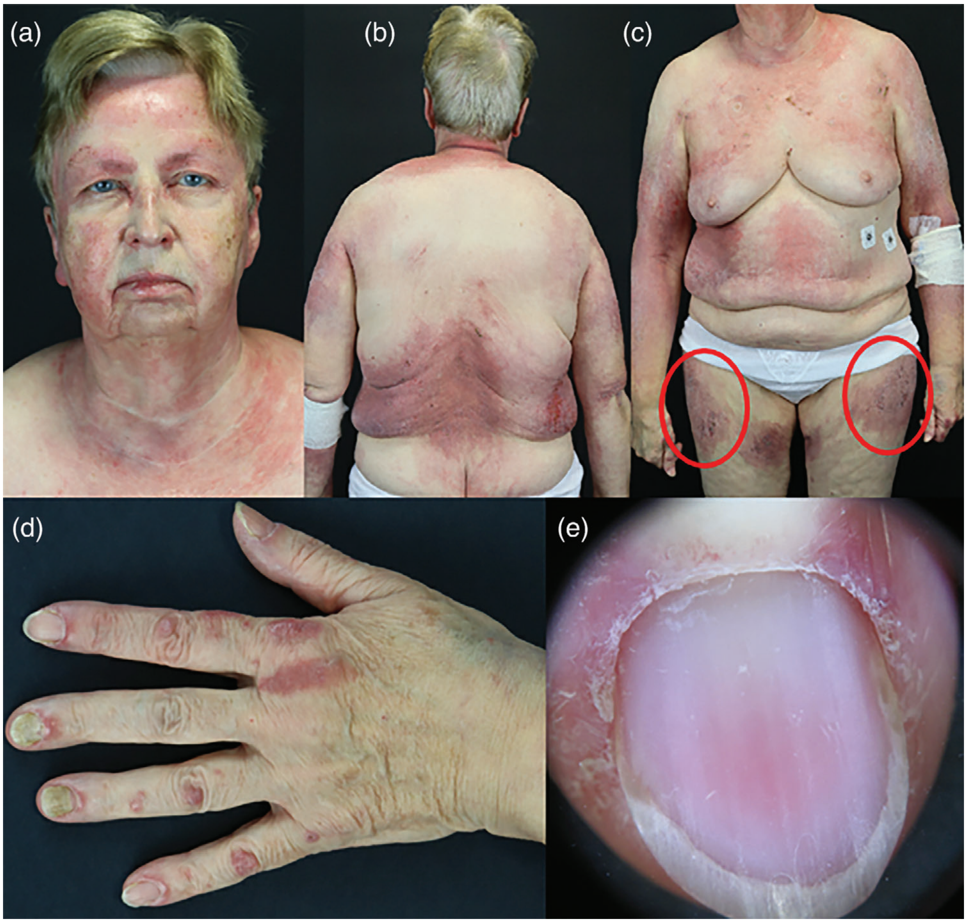

**FIGURE 4** New onset of dermatomyositis one week after the second mRNA-based SARS-CoV-2 vaccination. (a) Heliotrope erythema of the face and heliotrope rash on the chest (V-sign). Both are characteristic for dermatomyositis. (b) Erythematous rash on the lower back. (c) Erythematous rash on the chest and abdomen with violaceous erythema on the lateral thighs (Holster sign; see circles). (d) Erythematous papules over the knuckles and the intermediate phalanges of the left hand (Gottron papules). Gottron papules are pathognomonic for dermatomyositis. (e) Nail-fold changes characterized by periungual telangiectasia, hypertrophy of the cuticle, and small hemorrhagic infarcts (Keining's sign).

**TABLE 5** Meta-analysis of lichen planus after SARS-CoV-2 vaccination.

| Vaccination | Vaccine type | ø Days until flare | New-onset diagnosis (number of patients) | Pre-existing diagnosis (number of patients) | Total patients |
|---|---|---|---|---|---|
| First | mRNA | 8 | 5 (1 x vitiligo) | – | 5 |
| | AstraZeneca | 7 | 3 | – | 3 |
| | Others | 3 | – | 1 | 1 |
| Second | mRNA | 7 | 3 (1 x vitiligo) | 2 | 5 |
| | AstraZeneca | 11 | 1 | – | 1 |
| Data without further information | mRNA | ? | ? | ? | 4 |

Based on MEDLINE until the 30th of June 2022 with searching terms "COVID-19 vaccine lichen ruber planus" and "SARS-CoV-2 vaccine lichen ruber planus."

(approximately 96%) showed a new onset of leukocytoclastic vasculitis (LV), one patient had a previous history of LV and in three cases more information were not provided. The time interval between vaccination and onset of the skin lesions ranged between one and ten days.

A 68-year-old male patient with a new-onset LV was admitted in our department. He showed a palpable purpura on both lower and upper legs, as well as on the flanks. The patient reported that the purpura begun three days after the third SARS-CoV-2 vaccination (Moderna). After a

**TABLE 6** Meta-analysis of leukocytoclastic vasculitis after SARS-CoV-2 vaccination.

| Vaccination | Vaccine type | ø Days until flare | New-onset diagnosis (number of patients) | Pre-existing diagnosis (number of patients) | Total patients |
|---|---|---|---|---|---|
| First | mRNA | 4 | 5 | – | 5 |
| | AstraZeneca | 6 | 8 | – | 8 |
| | Janssen | 10 | 1 | – | 1 |
| | Others | 6 | 3 | – | 3 |
| Second | mRNA | 5 | 4 | 1 | 5 |
| | AstraZeneca | 5 | 4 | – | 4 |
| | Others | 5 | 1 | – | 1 |
| Third | mRNA | 2 | 1 | – | 1 |
| Data without further information | mRNA | ? | ? | ? | 3 |

Based on MEDLINE until the 30th of June 2022 with searching terms "COVID-19 vaccine leukocytoclastic vasculitis" and "SARS-CoV-2 vaccine leukocytoclastic vasculitis."

treatment with oral prednisolone, the skin lesions improved rapidly.

## DISCUSSION

The presence of a correlation between SARS-CoV-2 vaccination and a new onset or relapse of autoimmune skin diseases is still controversial. In the last few years, there has been a debate on the causality between vaccines and the onset or aggravation of autoimmune diseases. Indeed, tetanus toxoid, influenza, and polio vaccines, as well as others, have been found to have an influence on autoantibody formation and on development of autoimmune diseases, such as rheumatoid arthritis, BP, PV, autoimmune myositis, and SLE.[8–11] In addition, influenza vaccines have been reported to cause a transient flare in approximately 19.4% of SLE patients within six weeks.[12] In addition, there are some reported cases of SLE onset after vaccination against hepatitis B, tetanus, and typhoid fever.[13] Furthermore, it has been widely reported that mRNA-based SARS-CoV-2 vaccines activate the immune system in a non-specific manner.[14] Indeed, mRNA-based SARS-CoV-2 vaccine can increase type I interferon (IFN) production and trigger RNA sensors, such as Toll-like receptor 7, and components of the inflammasome, such as melanoma differentiation-associated protein 5 (MDA5) and nucleotide-binding oligomerization domain-containing protein 2 (NOD2).[15] However, flares or new onset of autoimmune diseases are rare and likely close to the background incidence of these conditions.[16] In addition, some reports have suggested that mRNA-based SARS-CoV-2 vaccines may influence the development of inflammatory skin diseases.[17,18]

The mechanism of autoimmune reactions following vaccination is still unclear. On the one hand, a genetic predisposition to vaccine-induced autoimmunity has been suggested, since only few subjects developed autoimmune diseases after vaccinations.[10] On the other hand, through immune cross-reactivity, due to the similarity between some vaccine components and specific human proteins, the immune system could induce autoimmune diseases (molecular mimicry).[10] Furthermore, activation of toll-like receptors on antigen-presenting cells has been postulated to play a role in the new onset of autoimmune diseases after vaccination.[19]

In summary, there is suggestive evidence that new onset or worsening of autoimmune skin disease is associated with SARS-CoV-2 vaccination. In fact, as described above, some patients from our clinic showed a significant worsening or new onset of autoimmune disease after SARS-CoV-2 vaccination. Accordingly, the meta-analysis performed for six autoimmune and inflammatory skin diseases lend support to our hypothesis. To reduce the bias of new diagnoses or worsening of diseases occurring independently of vaccination, the meta-analysis considered only individual cases that occurred up to a maximum of 21 days after SARS-CoV-2 vaccination. Furthermore, no difference between vector-based vaccines and mRNA-based vaccines with regard to new onset or exacerbation of the evaluated autoimmune disorders were detected. In general, the number of *de novo* or relapsing autoimmune skin diseases is higher for mRNA-based vaccines. As mRNA-based vaccines have been used more frequently than vector-based or other vaccines (grouped here under "others"), this observation may be biased. In some cases, patients received different SARS-CoV-2 vaccinations. Since the overall incidence of autoimmune diseases in the SARS-CoV-2 vaccinated population is low, no significant conclusion can be drawn about the type of SARS-CoV-2 vaccine and the association with more or fewer adverse events. The real number of new onset or worsening of autoimmune skin diseases after SARS-CoV-2 vaccination may be underestimated.

Regarding BP and LP, it can be reasonably postulated that the high number of reports is due to the prevalence of these diseases in the general population. Since LV is a common disease, the number of reports could possibly be underestimated due to the lack of interest about this skin disorder. Regarding PV, we reported an exacerbation in seven cases and a new onset in eight cases out of a total of

15 patients. This suggests that there is no significant difference between the two groups. Regarding DM, it has been reported that the immune response to the SARS-CoV-2 vaccination is similar to that elicited in this skin disease, and especially in DM patients with anti-MDA5 antibodies.[20,21] The higher prevalence of new onset DM compared to exacerbations may be related to ongoing immunosuppressive therapy in patients with a previous diagnosis of DM, which can prevent the activation of an overreacting autoimmune response. Indeed, the immune response to the SARS-CoV-2 vaccination has been found to be quite similar to the that reported in patients with DM, and especially those with positive anti-MDA5 antibodies.[20,21] However, it should be noted that for the most of the cases reported in the literature, we could not find further details (Table 4).

Regarding SLE, both molecular mimicry and activation of toll-like receptors on antigen-presenting cells have been postulated to play a role in new onset of the disease after SARS-CoV-2 vaccination.[19] Also in this case, the higher prevalence of new-onset SLE in comparison to exacerbations may be related to immunosuppressive therapies in patients with a previous diagnosis, which can reduce the risk of an overreacting activation of the immune system. However, it should be noted that we could not find more detailed information for the majority of the cases (Table 3).

In our patient with new onset of DM after SARS-CoV-2 vaccination, it should be noted that she had a previously undiagnosed cecal carcinoma. A correlation between the development of the skin features (Figure 4) and the SARS-CoV-2 vaccination can be assumed, but a coincidental onset of the disease cannot be excluded. Indeed, a paraneoplastic DM most likely developed simultaneously with the underlying neoplasia.[22] In this particular case, SARS-CoV-2 vaccination could be considered an aggravating factor.

In conclusion, new onset or worsening of skin autoimmune disorders associated with SARS-CoV-2 vaccination was observed in a few cases. Although vaccinations have been associated with aggravation and new onset of autoimmune diseases, several observations suggest that vaccinations are not linked to a greater risk of *de novo* manifestation or worsening of an already existing autoimmune disease than other trigger factors, such as drugs, bacterial, and viral infections.[23] Since vaccination saves many lives worldwide and induction or worsening of autoimmune disease is rarely observed, there is no reason to avoid vaccinations.[21] Especially in patients with autoimmune diseases on immunosuppressive therapy, vaccination against SARS-CoV-2 is strongly recommended.[24,25]

## INFORMED CONSENT

All patients gave their written informed consent for the publication of photos.

## ACKNOWLEDGMENT

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## CONFLICT OF INTEREST

None.

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